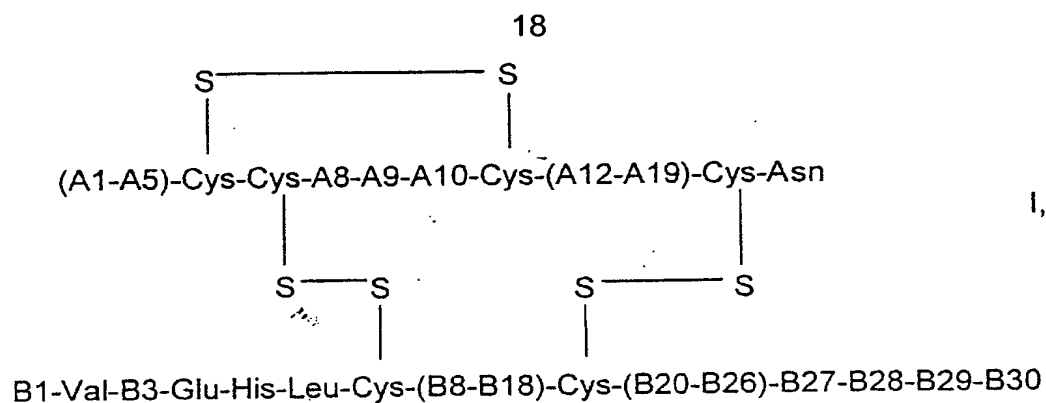


We claim:

1. A crystal of an insulin analog, in which asparagine (Asn) in position B3 of the B chain is replaced by a naturally occurring basic amino acid residue and at least one amino acid residue in the positions B27, B28 or B29 of the B chain is replaced by another naturally occurring neutral or acidic amino acid residue, where phenylalanine (Phe) in position B1 of the B chain can optionally be absent, the crystals being present in the space group R3 (No. 146) with the cell axes  $A = 81.5 \text{ \AA} \pm 1 \text{ \AA}$  and  $C = 33.3 \text{ \AA} \pm 1 \text{ \AA}$ .
2. The crystal of Claim 1, wherein the molecules of the insulin analog are present in the form of the zinc-free hexamers consisting of in each case three dimers.
3. The crystal of Claim 2, wherein the histidine B10 residues of in each case three molecules of the insulin analog in a hexamer are bonded to a water molecule via hydrogen bonds.
4. The crystal of Claim 2, wherein the histidine B10 residues of in each case three molecules of the insulin analog in a hexamer are bonded to a dihydrogenphosphate ion ( $\text{H}_2\text{PO}_4^-$ ) via hydrogen bonds.
5. The crystal of Claim 2, wherein the histidine B10 residues of in each case three molecules of the insulin analog in a hexamer are bonded to a monohydrogenphosphate ion ( $\text{HPO}_4^{2-}$ ) via hydrogen bonds.
6. The crystal of Claim 2, wherein the histidine B10 residues of in each case three molecules of the insulin analog in a hexamer are bonded to a sulfate ion ( $\text{SO}_4^{2-}$ ) via hydrogen bonds.
7. The crystal of Claim 1, wherein the histidine B10 residues of the molecules of the insulin analog in a hexamer are in each case folded back onto their own dimer and no hydrogen bond formation of the histidine B10 residues to a water molecule is present.
8. The crystal of Claim 1, wherein the insulin analog is a compound of formula I,



in which

- |    |                     |   |
|----|---------------------|---|
| 5  | (A1-A5)             | are the amino acid residues in the positions A1 to A5 of the A chain of human insulin or animal insulin,  |
|    | (A8-A10)            | are the amino acid residues in the positions A8, A9 and A10 of the A chain of human insulin or animal insulin,  |
| 10 | (A12-A19)           | are the amino acid residues in the positions A12 to A19 of the A chain of human insulin or animal insulin,  |
| 15 | (B8-B18)            | are the amino acid residues in the positions B8 to B18 of the B chain of human insulin or animal insulin,   |
|    | (B20-B26)           | are the amino acid residues in the positions B20 to B26 of the B chain of human insulin or animal insulin,  |
| 20 | (B30)               | is the amino acid residue in position B30 of the B chain of human insulin or animal insulin,  |
|    | B1                  | is a phenylalanine residue (Phe) or a hydrogen atom,  |
| 25 | B3                  | is a naturally occurring basic amino acid residue,  |
|    | B27, B28<br>and B29 | are the amino acid residues in the positions B27, B28 and B29 of the B chain of human insulin or animal insulin or in each case another naturally occurring amino acid residue, |
| 30 |                     | where at least one of the amino acid residues in the positions B27, B28 and B29 of the B chain is replaced by another   |

naturally occurring amino acid residue which is selected from the group consisting of the neutral or acidic amino acids.

9. The crystal of Claim 8, wherein the amino acid residue in position B3  
5 of the B chain of the insulin analog is a histidine (His), lysine (Lys) or arginine residue (Arg).

10. The crystal of Claim 8, wherein at least one of the amino acid  
10 residues in the positions B27, B28 and B29 of the B chain is a naturally occurring amino acid residue which is selected from the group consisting of isoleucine (Ile), aspartic acid (Asp) and glutamic acid (Glu).

11. The crystal of Claim 10, wherein the B chain has the sequence  
15 Phe Val Lys Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu  
Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Glu Thr  
(SEQ ID NO 3).

20 12. A pharmaceutical preparation comprising at least one crystal of Claim 1.

13. The pharmaceutical preparation of Claim 12 further comprising an  
25 excipient which facilitates the absorption of the insulin analog into the blood.

14. The pharmaceutical preparation of Claim 12 further comprising an  
excipient, which is used in inhalative and/or oral formulations of insulin or  
insulin analogs.

30 15. The use of one or more crystals of Claim 1 for the production of a pharmaceutical preparation which has an insulin activity having a rapid onset of action.

35 16. A process for the preparation of one or more crystals of Claim 1 comprising the steps of:

- (a) dissolving a zinc-free, amorphous powder of the insulin analog of Claim 1 in a concentration of 15-25 mg/ml;
- (b) precipitating the crystal using a suitable precipitant; and

(c) isolating and drying the crystals.

17. The process of Claim 16, wherein the insulin analog is Lys B3, Glu B29-human insulin.

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18. The process of Claim 16, wherein the suitable precipitant is selected from the group consisting of:

- (a) ammonium dihydrogenphosphate,
- (b) a combination of ammonium dihydrogenphosphate and trisodium citrate; and
- (c) a combination of ammonium sulfate and polyethylene glycol of various molecular weights.

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19. The process of Claim 18, wherein the suitable precipitant used is selected from the group consisting of ammonium dihydrogenphosphate or diammonium hydrogenphosphate at a pH of between 3.0 and 8.0.

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20. The process of Claim 18, wherein the suitable precipitant used is selected from the group consisting of ammonium dihydrogenphosphate/diammonium hydrogenphosphate in combination with trisodium citrate at a pH of  $5.5 \pm 1.5$  or ammonium sulfate in combination with PEG of various molecular weights at a pH of  $6.0 \pm 1.5$ .

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21. The use of one or more crystals of Claim 1 for the production of a pharmaceutical for the treatment of diabetes of types I and/or II.

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22. A method of treating Type I or Type II diabetes comprising administering to a patient in need thereof a therapeutically effective amount of one or more crystals of Claim 1.

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